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415

We claim:

1. A method for producing a human sequence immunoglobulin polypeptide comprising the steps:
(A) obtaining a transgenic mouse, wherein said transgenic mouse comprises a homozygous pair of functionally disrupted endogenous heavy chain alleles, a homozygous pair of functionally disrupted endogenous light chain alleles, at least one copy of a human immunoglobulin light chain transgene, and at least one copy of a human immunoglobulin heavy chain transgene;
(B) immunizing the transgenic mouse with a predetermined antigen, wherein an immune response is induced and whereby a transgene of the mouse undergoes V-D-J rearrangement, whereby a rearranged transgene is produced;
(C) isolating and sequencing a nucleic acid encoding at least a portion of a variable region of the rearranged transgene, and determining the amino acid sequence of an immunoglobulin polypeptide encoded by the sequenced portion of the rearranged transgene;
(D) making an artificial gene that encodes a second immunoglobulin polypeptide, wherein the second immunoglobulin polypeptide comprises an amino acid sequence that is substantially similar to the amino acid sequence of the immunoglobulin polypeptide encoded by the sequenced portion of the rearranged transgene;
(E) linking the artificial gene to a transcription promoter sequence; and
(F) introducing the artificial gene into a cell;
whereby a human sequence immunoglobulin polypeptide is produced.

2. The method of claim 1 wherein the second immunoglobulin polypeptide comprises an amino acid sequence that is the same as the amino acid sequence of the immunoglobulin polypeptide encoded by the sequenced portion of the rearranged transgene.

3. The method of claim 1 wherein the nucleic acid of step (c) is isolated from a hybridoma secreting a human sequence immunoglobulin.

4. The method of claim 1 wherein the rearranged transgene is a human immunoglobulin heavy chain transgene.

5. The method of claim 4 wherein the artificial gene encodes a gamma isotype constant region.

6. The method of claim 4, further comprising introducing a second artificial gene into the cell of step (F), wherein the second artificial gene is made according to steps A-E of claim 4 except that the rearranged transgene is a

human immunoglobulin light chain transgene, and wherein the cell produces an immunoglobulin.

7. The method of claim 6 wherein the human immunoglobulin heavy chain transgene and the human immunoglobulin light chain transgene are expressed in a hybridoma produced by fusing a single B cell from a transgenic mouse to an immortal cell.

8. The method of claim 6 wherein the cell produces an immunoglobulin that binds the predetermined antigen with an affinity constant (K_a) of at least about 10^8 M^{-1}.

9. An immunoglobulin produced by the method of claim 1.

10. A cell comprising at least one artificial gene encoding at least a portion of an immunoglobulin polypeptide, wherein the cell produces a detectable amount of an immunoglobulin that binds a predetermined human antigen, and wherein the immunoglobulin polypeptide has substantially the same sequence as an immunoglobulin polypeptide secreted by a hybridoma obtained from a transgenic mouse, said mouse comprising a homozygous pair of functionally disrupted endogenous heavy chain alleles, a homozygous pair of functionally disrupted endogenous light chain alleles, at least one copy of a human immunoglobulin light chain transgene, and at least one copy of a human immunoglobulin heavy chain transgene.

11. A eukaryotic cell of claim 10.

12. The cell of claim 11 wherein the immunoglobulin binds human CD4 or an antigenic fragment thereof.

13. An immunoglobulin that specifically binds human CD4, wherein said immunoglobulin comprises a human sequence light chain variable region comprising an amino acid sequence substantially identical to an amino acid sequence encoded by Seq. I.D. No. 1, Seq. I.D. No. 2, Seq. I.D.No. 3, Seq. I.D. No. 4, Seq. I.D. No. 5, Seq. I.D. No. 6, Seq. I.D. No. 7, Seq. I.D. No. 8, Seq. I.D. No. 9, or Seq. I.D., No. 10.

14. The immunoglobulin of claim 13 wherein the immunoglobulin comprises the sequence of Seq. I.D. No. 61 or Seq. I.D. No. 62.

15. A method for selecting a hybridoma secreting a human sequence immunoglobulin that specifically bind a preselected antigen comprising the steps:
a) obtaining B cells from a trangenic mouse, wherein the transgenic mouse comprises a homozygous pair of functionally disrupted endogenous heavy chain alleles, a homozygous pair of functionally disrupted endogenous light chain alleles, at least one copy of

a human immunoglobulin light chain transgene, and at least one copy of a human immunoglobulin heavy chain transgene comprising sequences encoding μ and non-μ segments, and wherein the mouse has been immunized with the predetermined antigen;

b) fusing the B cells to immortal cells wherein hybridomas are produced;

c) identifying a first group of hybridomas that secrete non-μ, non-δ isotype immunoglobulins;

d) identifying a second group of hybridomas, wherein the second group is a subset of the first group of hybridomas, and wherein hybridomas in the second secrete immunoglobulins that specifically bind the predetermined antigen;

e) selecting from the second group of hybridomas a hybridoma secreting a human sequence immunoglobulin that specifically binds to the preselected antigen.

16. The method of claim 15 wherein the first group of hybridomas secrete IgG immunoglobulins.

17. The method of claim 15 wherein the human sequence immunoglobulin of step (e) binds the predetermined antigen with an affinity constant (K_a) of at least about 10^9 M^{-1}.

18. A human anti-CD4 immunoglobulin that specifically binds CD4 from humans and specifically binds CD4 from at least one non-human primate.

19. The immunoglobulin of claim 18 wherein the non-human primate is Rhesus monkey, cynomolgus monkey, or chimpanzee.

20. The immunoglobulin of claim 19 wherein the human anti-CD4 immunoglobulin specifically binds CD4 from both rhesus monkey and cynomolgus monkey.

21. The immunoglobulin of claim 19 wherein the human anti-CD4 immunoglobulin specifically binds CD4 from rhesus monkey, cynomolgus monkey and chimpanzee.

22. A human sequence immunoglobulin comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH [Seq. I.D. No. 63].

23. A human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH2 segment, and a heavy chain CDR3 region comprising the sequence PANWNWYFVL [Seq. I.D. No. 64].

24. A human sequence immunoglobulin comprising a VH4-34 segment, a JH5 segment, and a heavy chain CDR3 region comprising the sequence VINWFDP [Seq. I.D. No. 65].

25. A human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH4 segment , and a heavy chain CDR3 region comprising the sequence DQLGLFDY [Seq. I.D. No. 66].

26. A human sequence immunoglobulin comprising a VkA27/A11 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQYGSSPLT [Seq. I.D. No. 67].

27. A human sequence immunoglobulin comprising a VkL18 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQFISYPQLT [Seq. I.D. No. 68].

28. A human sequence immunoglobulin comprising a VkL19 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQANSFPYT [Seq. I.D. No. 69].

29. A human sequence immunoglobulin comprising a VkL15 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQYDSYPYT [Seq. I.D. No. 70].

30. A hybridoma secreting an immunoglobulin, wherein the immunoglobulin is selected from the group consisting of: a human sequence immunoglobulin comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH [Seq. I.D. No. 63], a human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH2 segment, and a heavy chain CDR3 region comprising the sequence PANWNWYFVL [Seq. I.D. No. 64], a human sequence immunoglobulin comprising a VH4-34 segment, a JH5 segment, and a heavy chain CDR3 region comprising the sequence VINWFDP [Seq. I.D. No. 65], a human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH4 segment , and a heavy chain CDR3 region comprising the sequence DQLGLFDY [Seq. I.D. No. 66], a human sequence immunoglobulin comprising a VkA27/A11 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQYGSSPLT [Seq. I.D. No. 67], a human sequence immunoglobulin comprising a VkL18 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQFISYPQLT [Seq. I.D. No. 68], a human sequence immunoglobulin comprising a VkL19 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQANSFPYT [Seq. I.D. No. 69], and a human sequence immunoglobulin comprising a VkL15 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQYDSYPYT [Seq. I.D. No. 70].